70. (New) The method of claim 65, wherein a first portion of medicament is granulated with said sustained release granulate, and a second portion of medicament is added extragranularly.

71. (New) The method of claim 65, wherein said sustained release granulate is prepared by dry granulation.

72. (New) The method of claim 65, wherein said sustained release granulate is prepared by wet granulation.

REMARKS

Claims 1-13 and 15-72 are pending. Claims 1, 15-16, 21, 24, 42, 43, 45, 46 and 61 have been amended. Claim 14 has been cancelled, without prejudice. Support for new claims 65-72 can be found in the specification on page 7, lines 13-19 and 29-30 through page 8, lines 1-3; page 12, lines 1-5; page 13, lines 14-16; and page 17, lines 25-30. Applicants respectfully submit that no new matter has been added by virtue of these amendments.

I. REJECTION UNDER 35 U.S.C. § 102

In the Office Action, the Examiner rejected claims 1-3, 6-9, 13, 21-25, 32-44 and 61-64 under 35 U.S.C. § 102(b) as being anticipated by Baichwal et al. (U.S. 5,399,359, hereinafter "the '359 patent"). The Examiner stated that the '359 patent "discloses oxybutynin xanthan gum/locust bean gum sustained release compositions comprising a pH modifying agent such as sodium carbonate or sodium bicarbonate...The compositions provide sustained release at least about 24 hours and are in ratios within the instant ranges."

Amended independent claims 1 and 61 recite in pertinent part "a sustained release oral solid dosage form comprising ... a pH modifying agent comprising an organic acid."

In the Office Action, the Examiner admits that the '359 patent "does not teach the limitation where the pH modifying agent is an organic acid." As both independent claims 1 and 61 as amended require "a pH modifying agent comprising an organic acid," these claims cannot be anticipated by the '359 patent. Further as claims 2-13 and 15-44 depend from claim 1; and claims 62-64 depend from claim 61, the dependent claims are also not anticipated by the '359 patent. Withdrawal of the rejection is therefore requested.

Similarly, new independent claim 65 and claims 66-72, which depend from claim 65, also recite "a pH modifying agent comprising an organic acid" and therefore cannot be anticipated by the '359 patent.

II. REJECTION UNDER 35 U.S.C. § 103(a)

In the Office Action, the Examiner also rejected claims 1-13, 17, 21-25, 32-44, and 61-64 under 35 U.S.C. § 103(a) as being unpatentable over the '359 patent by contending, in addition to his argument set forth above, that "manipulation of the amounts of ingredients such as the pH modifying agent would have been obvious to one skilled in the art at the time of the invention to increase or decrease the degree of cross-linking of the polysaccharides." As discussed above, there is no teaching or suggestion in the '359 patent of organic acids for use as pH modifying agents as claimed in the present invention. The '359 patent discloses the use of a cationic cross-linking agent (e.g., sodium carbonate or sodium bicarbonate), which is capable of cross-linking with the gelling agent to increase the gel strength of the formulation to prevent an initial "burst" of drug release from the dosage formulation. The '359 patent does not teach, hint or suggest the use of organic acids, let alone as a pH modifying agent to facilitate the release of the medicament from the dosage form to provide for a high bioavailability. Accordingly, independent claims 1 and 61 are not obvious in view of the '359

patent. As claims 2-13 and 15-44 depend from claim 1; and claims 62-64 depend from claim 61, the dependent claims are also not obvious over the '359 patent. Therefore, Applicants respectfully request that the Examiner's § 103 rejection over the '359 patent be removed.

Similarly, new independent claim 65 and claims 66-72, which depend from claim 65 recite "a pH modifying agent comprising an organic acid" and therefore are also not obvious in view of the '359 patent.

In the Office Action, the Examiner further rejected claims 1-13, and 18-64 under 35 U.S.C. § 103(a) as being unpatentable over the '359 patent in view of Baichwal et al. (U.S. 5,478,574, hereinafter "the '574 patent"). The Examiner stated that the '359 patent "is relied upon for all that it teaches as stated previously...'574 teaches inclusion of a surfactant in xanthan gum/locust bean gum compositions provides a bimodal or multi-phase controlled release of a therapeutically active ingredient... [and] also teaches that such xanthan gum/locust bean gum compositions are effective for delivering active agents such as diltiazem...Accordingly, it would have been obvious to one skilled in the art at the time of the invention to combine the '359 and '574 to achieve bimodal or multi-phase controlled release of a therapeutically active ingredient."

The '574 patent is cited by the Examiner merely for its purported inclusion of a surfactant. As noted, amended independent claims 1 and 61 of the present invention recite "a pH modifying agent comprising an organic acid." Amended independent claim 46 also recites "a pH modifying agent comprising an organic acid." As explained above, there is no teaching or suggestion in the '359 patent of the use of organic acids as claimed in the present invention. The '574 patent also does not teach or suggest the use of organic acids, let alone as pH modifying agents. As such, the '574 patent cannot cure the deficiencies of the '359 patent. Accordingly, independent claims 1 and 61 are not obvious over the '359 patent in view of the '574 patent. As claims 2-13 and 15-44 depend from claim 1; claims 47-60 depend from claim 46; and claims

62-64 depend from claim 61, the dependent claims are also not obvious over the '359 patent in view of the '574 patent. Therefore, it is respectfully requested that the Examiner's § 103 rejection over the '359 patent in view of the '574 patent be removed.

Similarly, new independent method claim 65 and claims 66-72, which depend from claim 65 also recite "a pH modifying agent comprising organic acids." Therefore these new claims are also not obvious over the '359 patent in view of the '574 patent.

In the Office Action, the Examiner rejected claims 1-17, 21-25, 32-44 and 61-64 under 35 U.S.C. § 103(a) as being unpatentable over the '359 patent in view of Panoz et al. (U.S. 4,726,951, hereinafter "the '951 patent"). The Examiner stated that the '359 patent "does not teach the limitation where the pH modifying agent is an organic acid....'951 is relied upon for teaching inclusion of organic acids in pharmaceutical compositions to modify pH and maintain optimum absorption conditions for an active agent." The Examiner therefore asserted that it would have been obvious to one skilled in the art at the time of the invention to combine the '359 and '951 patents to maintain optimum absorption conditions for an active agent.

The '951 patent purportedly describes a medicament for oral use comprising an association of a) miniaturized granules having a central core surrounded by several layers containing a mixture of one or more active ingredients with an active excipient containing a physiologically active neutralization agent for controlling the pH, the layers of active ingredient being separated from each other by layers of excipient which determine the slow penetration of the alimentary and digestive liquids; b) miniaturized granules containing one or more active ingredients coacted with excipients determining the slow penetration of digestive and alimentary liquids; and c) miniaturized granules containing one or more active ingredients coated with a very thin layer of lipids, the proportion or each of the types of miniaturized granules defined in a), b) and c) varying from 0-100%. According to the '951 patent, the possibility of controlling the release of active medicament all along the path of the gastrointestinal tract presupposes that

the solubility of the medicament can be controlled at each instance of this progression. Further, according to the '951 patent, by choosing neutralization agents having different solubilities, the '951 patent provides for a neutralization delay phenomenon, whereby the varying solubilities cause the neutralization agents to relay each other while the active ingredient travels along the gastrointestinal tract, thus maintaining optimum absorption of a medicament throughout the entire gastrointestinal tract. The '951 patent additionally states that the amount of organic acids which form the neutralization agent, in relation to the active ingredient, increases from the layers on the central core to the peripheral layers of the miniaturized granules, thus forming a miniaturized granule with a pH gradient (see: col. 2, line 40 through col. 5, line 2).

Amended independent claims 1 and 61 of the present invention recite sustained release dosage forms comprising a mixture of... a medicament, a pH modifying agent comprising an organic acid and a sustained release granulate comprising a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum. The compressed miniaturized granules described in the '951 patent do not contain a sustained release granulate comprising a heteropolysaccharide gum and a homopolysaccharide gum as recited in the claims of the present invention. The '951 patent describes the use of neutralization agents, e.g., organic acids, for providing a pH gradient throughout the layers of miniaturized granules. The '359 patent is directed towards sustained release matrix dosage forms. One skilled in the art would not look to the layered microparticles of the '951 patent to improve on the matrix formulations of the '359 patent. Thus, one skilled in the art would not be motivated to combine the '359 and '951 patents. Even if the '359 and '951 patents were combined, the skilled artisan would still not use the organic acid in the manner of the present invention to facilitate the release of medicament from the dosage form. Accordingly, amended independent claims 1 and 61 are not obvious over the '359 patent in view of the '951 patent. As claims 2-13 and 15-44 depend from claim 1 and claims 62-64 depend from claim 61, the dependent claims are also not obvious over the '359 patent in view of the '951 patent. Therefore, Applicants respectfully request that the Examiner's § 103 rejection be removed.

Similarly, new independent claim 65 and claims 66-72, which depend from claim 65 recite methods of preparing the sustained release dosage form of independent claims 1 and 61, therefore these claims are also not obvious over the '359 patent in view of the '951 patent.

In the Office Action, the Examiner rejected claims 1-17, 21-25, 32-44 and 61-64 under 35 U.S.C. § 103(a) as being unpatentable over the '359 patent in view of Baichwal et al. (WO 97/26865, hereinafter "the '865 patent"). The Examiner stated that '359 patent "does not teach the limitation where the pH modifying agent is an organic acid... '865 is relied upon for teaching inclusion of organic acids in xanthan gum/locust bean gum compositions as strength enhancing agents... '865 does not explicitly teach combining two strength enhancing agents, however, it would have been obvious to one skilled in the art at the time of the invention to do so to provide an additive effect of enhanced strength."

The '865 patent is cited by the Examiner for its purported inclusion of organic acids in xanthan gum/locust bean gum compositions as strength enhancing agents. The use of organic acids as gel strength enhancing agents in the '865 patent provides for an increase in gel strength when the homopolysaccharide is exposed to an aqueous environment, thus preventing an initial "burst" of drug release from the formulation. Although the '865 patent describes the use of organic acids as gel strength enhancing agents for providing an increase in gel strength when the homopolysaccharide is exposed to an aqueous environment, it does not teach, hint or suggest the use of a pH modifying agent comprising an organic acid to facilitate the release of a medicament from a dosage form, as recited in amended independent claims 1 and 61 of the present invention. As such, one skilled in the art would not have been motivated to combine the teachings of the '865 patent with the teachings of the '359 patent. Even if the '359 and '865 patents were combined, one skilled in the art would still not arrive at the present invention, as the organic acids described in the '865 patent are incorporated into the sustained release excipient. In contrast, in amended independent claims 1 and 61, the pH modifying agent comprising an organic acid of the present invention is not incorporated into the sustained release granulate, but

instead is added after the sustained release excipient has been prepared. Accordingly, amended independent claims 1 and 61 are not obvious over the '359 patent in view of the '865 patent. As claims 2-13 and 15-44 depend from claim 1 and claims 62-64 depend from claim 61, the dependent claims are also not obvious over the '359 patent in view of the '865 patent. Therefore, Applicants respectfully request that the Examiner's § 103 rejection be removed.

Similarly, new independent method claim 65 and claims 66-72 also do not incorporate the pH modifying agent comprising an organic acid into the sustained release granulate, therefore, new method claims 65-72 are also not obvious over the '359 patent in view of the '865 patent.

In the Office Action, the Examiner rejected claims 1-17, 21-25, 32-44 and 61-44 under 35 U.S.C. § 103(a) as being unpatentable over the '359 patent in combination with the '574 patent and in further combination with the '865 patent. The Examiner stated that "the '359, '574, and '865 are all relied upon for all that they teach as previously stated...It would have been obvious to one skilled in the art at the time of the invention to combine the teachings of these references to provide sustained release compositions comprising xanthan gum/locust bean gum that is strong and has a bimodal or multi-phase controlled release profile of an active agent."

In response, for the reasons stated above, Applicants respectfully submit that the '359, '574 and '865 patent do not render the present invention obvious. The '359 patent does not teach, hint or suggest the use of organic acids as pH modifying agents as claimed in the present invention. As discussed above, the '574 patent also does not teach or suggest the use of organic acids, let alone as pH modifying agents. As such, the '574 patent cannot cure the deficiencies of the '359 patent. Furthermore, as discussed above, the '865 patent describes the use of organic acids as gel strength enhancing agents that provide for an increase in gel strength when the homopolysaccharide is exposed to an aqueous environment, thus preventing an initial "burst" of drug release from the formulation. The organic acids described in the '865 patent are incorporated into the sustained release excipient, as opposed to being added together with the

medicament after the sustained release excipient has been prepared as disclosed by the present invention. As such, one skilled in the art would not have been motivated to combine the teachings of the '865 patent with the teachings of the '359 patent. Even if the '359, '574 and '865 patents were combined, one skilled in the art would still not arrive at the present invention. Accordingly, amended independent claims 1 and 61 are not obvious over the '359 patent in view of the '574 and '865 patents. As claims 2-13 and 15-44 depend from claim 1 and claims 62-64 depend from claim 61, the dependent claims are also not obvious over the '359 patent in view of the '574 and '865 patents. Therefore, Applicants respectfully request that the Examiner's § 103 rejection be removed.

Similarly, new independent method claim 65 and claims 66-72, which depend from claim 65 recite a pH modifying agent comprising an organic acid and therefore are also not obvious over the '359 patent in view of the '574 and '865 patents.

CONCLUSION

Applicants respectfully submit that in view of the arguments made, the pending claims are in condition for allowance.

A check in the amount of $1148.00 is enclosed, $920.00 of which is to cover the fee under 37 C.F.R. § 1.136(a) for a three-month extension of time. The additional $228.00 is to cover additional claim fees. If it is determined that additional fees are due, or that any fee has been overpaid, the Assistant Commissioner is hereby authorized to deduct said fee or credit any overpayment to Deposit Account No. 50-0552.

Respectfully submitted,

DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____

Leslye B. Davidson
Reg. No. 38,854

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

Marked-Up Amended Claims

1. (Amended) A sustained release oral solid dosage form comprising a mixture of:

a [an] therapeutically effective amount of a medicament having a solubility of more than about 10 g/l;

a pH modifying agent comprising an organic acid; and

a sustained release [matrix] granulate, the sustained release granulate comprising a gelling agent, said gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid,

said dosage form providing a sustained release of said medicament after oral administration to human patients, said pH modifying agent facilitating the release of said medicament from said dosage form.

15. (Amended) The sustained release oral solid dosage form of claim [14] 1, wherein said organic acid is selected from the group consisting of citric acid, succinic acid, fumaric acid, malic acid, maleic acid, glutaric acid, lactic acid, and combinations thereof.

16. (Amended) The sustained release oral solid dosage form of claim [15] 1, wherein said organic acid is fumaric acid.

21. (Amended) The oral solid dosage form of claim 1, wherein said sustained release granulate [matrix] further comprises a hydrophobic material.

24. (Amended) The oral solid dosage form of claim 5, wherein said sustained release granulate [matrix] comprises from about 1 to about 20% by weight of said hydrophobic material.

42. (Amended) The oral solid dosage form of claim 40, wherein a sufficient amount of said granules to provide an effective dose of said medicament [are] is disposed in a pharmaceutically acceptable capsule.

43. (Amended) The oral solid dosage form of claim 39, wherein at least part of a surface of said tablet is coated with a hydrophobic material to a weight gain of from about 1 to about 20 percent, by weight.

45. (Amended) The sustained release oral dosage form of claim 18, which provides a bimodal absorption profile of said medicament.

46. (Amended) A sustained release oral solid dosage form comprising a mixture of:

an effective amount of a calcium channel blocker to provide a therapeutic effect, said calcium channel blocker having a solubility greater than 10 g/L;

a pH modifying agent comprising an organic acid;

a pharmaceutically acceptable surfactant; and

a sustained release [excipient] granulate, the sustained release granulate comprising a

gelling agent, said gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid,

said dosage form providing a bimodal absorption profile of said calcium channel blocker and providing a sustained release of said calcium channel blocker for at least about 12 hours after oral administration to human patients, said pH modifying agent facilitating the release of said medicament from said dosage form.

61. (Amended) A sustained release oral solid dosage form comprising a mixture of:

an effective amount of oxybutynin or a pharmaceutically acceptable salt thereof to provide a therapeutic effect[,] ;

a pH modifying agent comprising an organic acid; and

a sustained release [excipient] granulate, the sustained release granulate comprising a gelling agent, said gelling agent [comprises] comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum,

said dosage form providing a therapeutic effect for at least about 24 hours after administration to human patients, said pH modifying agent facilitating the release of said medicament from said dosage form.